A sustainable supply of pharmaceutical products for a healthy society

Act now and establish the legal framework

AOK Baden-Württemberg
Die Gesundheitskasse.

Executive Summary

A sustainable supply of pharmaceutical products for a healthy society – Act now and establish the legal framework

The political and public debate on the supply of pharmaceuticals is currently dominated by a debate on higher prices for and shortages of some of these products. However, the production and supply of pharmaceuticals is viewed from a too short-term and one-sided perspective. Long-term, serious developments, such as increasing antibiotic resistance, poor local production conditions and the negative impact on people and the environment, are barely taken into account.

There is no question that stable supply chains and sustainably fair and viable price reimbursement models are needed for a reliable supply of pharmaceuticals. Dependencies on global, non-European markets must also be minimised in order to reduce the risks of unstable supply chains and strengthen the resilience of the supply of pharmaceutical products.

However, the supply of pharmaceuticals can only be stabilised in the long term if it is made sustainable in all three aspects – economic, social and ecological. In this regard we have a responsibility as a society in general, both nationally and at European level.

Antimicrobial resistance (AMR) jeopardises the effective prevention and medical treatment of a steadily growing number of infections and leads to a high number of premature deaths worldwide. Both the EU Commission and the WHO categorise AMR as one of the greatest threats to health. These include, above all, antibiotic resistance. **As the most powerful weapon in the fight against infectious diseases, antibiotics are increasingly losing their effectiveness due to the development of resistance. One of the main reasons for this is the unhindered discharge of contaminated production wastewater and surface runoff into the immediate environment.** From a scientific point of view, there is no longer any doubt that a reduction in environmental pollution in bodies of water, for example via the entry route of active pharmaceutical ingredients production, will lead to a significant reduction in the emergence of multi-resistant pathogens.

The production, authorisation and reimbursement of pharmaceutical products are already subject to a high level of regulation in terms of efficacy, quality and availability. This applies at national, European and international level. However, it is clear that this regulatory framework is unnecessarily bureaucratic on the one hand, but on the other hand still falls short when it comes to ecological aspects, such as identifying and preventing the discharge of contaminated production wastewater from pharmaceutical production into the environment.

For this reason, AOK Baden-Württemberg (health insurance organisation), the Institute for Water Research (IWW) and the German Environment Agency (UBA) are investigating the environmental impact of antibiotic production on a scientific basis and in a hitherto unique form as part of pharmaceutical discount contracts. The experience already gained shows an urgent need for action that can no longer be ignored in political discussion.←

Introduction

Environmental impacts of pharmaceutical production and their consequences

Medical progress and pharmaceutical development are among the greatest achievements of the last century. Antibiotics and vaccines, for example, have made a significant contribution to extending life expectancy over the last 50 years. Unfortunately, antibiotics, the most powerful weapon in the fight against infectious diseases, are increasingly losing their effectiveness due to the emergence and spread of antibiotic resistance. **Worldwide, the incidence of disease caused by infections with antibiotic-resistant pathogens has risen sharply**. In January 2022, scientists published a study in The Lancet according to which multi-resistant germs are responsible for the majority of deaths worldwide.[1] Infections with an antibiotic-resistant pathogen were partly responsible for around 4.94 million deaths worldwide in 2019. 1.27 million deaths are directly attributable to such an infection. According to a study, around 54,500 people in Germany contract infections caused by antibiotic-resistant pathogens every year.[2] The incidence of disease caused by infections with antibiotic-resistant pathogens is therefore equivalent to the combined incidence of influenza, tuberculosis and HIV/AIDS. If no countermeasures are taken, the OECD estimates that the German healthcare system could be burdened with costs totalling 1.2 billion euros per year.[3]

Wastewater from manufacturing is a risk

In addition to the risk posed by the massive use of antibiotics in human and veterinary medicine, contaminated production wastewater is a major reason for the development of antibiotic resistance.[4, 5] If multi-resistant germs can spread in and via contaminated manufacturing wastewater, the effectiveness of antibiotics is severely jeopardised. This is **likely to have massive health, social and financial consequences for healthcare** worldwide.←

Pilot study

Research on ecological sustainability: Pilot study by the AOK Baden-Württemberg, the IWW Institute for Water Research and the German Environment Agency

As the first organisation of health insurance funds in Germany, the AOK, under the leadership of AOK Baden-Württemberg, has initiated and carried out a pilot study on environmental sustainability in antibiotic supply together with IWW and with the support of UBA starting in 2020. The aim of the pilot study is to create incentives for the environmentally friendly production of antibiotics through a voluntary bonus criterion as part of the awarding of discount contracts for pharmaceutical companies. The companies agree to comply with an effect-based maximum concentration („Predicted No Effect Concentration", PNEC) in the production wastewater and surface runoff of the active substance production site and allow an on-site inspection by the IWW.

Testing at ten sites

Since September 2021, a total of 21 tests have been carried out at ten sites in India and Europe. The water samples were measured at the IWW in Germany for the concentrations of the specified antibiotics contained in the (waste) water. The contracted antibiotics tested so far include roxithromycin, ciprofloxacin, moxifloxacin, amoxicillin, cefaclor and levofloxacin. The inspection took place in each case following a visit to the production sites at short notice. It included:

- Inspection of the wastewater treatment technologies used
- Joint inspection of the production site
- Sampling of wastewater from production at the end of the treatment chain and of surface runoff

In addition, water samples from the nearby environment affected by the production facilities were analysed for antibiotics.

If concentrations of the contracted antibiotics were found to have been exceeded in the production wastewater or surface runoff, the pharmaceutical companies were informed and made aware of this and requested to initiate improvements at the manufacturing sites. Follow-up samplings and subsequent analyses were also carried out.

The implementation and follow-up of the wastewater criterion through the cooperation between the AOK and the IWW is unique in Europe. The pilot study creates new transparency with regard to the ecological sustainability of active pharmaceutical ingredient synthesis as the starting point of global pharmaceutical supply chains.

→ Measurement results show risks to local population and risk of a global spread of antimicrobial resistance

At three production sites and at a water body directly affected by a fourth production site, threshold values for five of the contracted antibiotics were found to have been exceeded, in some cases massively.

The highest exceedance was found for ciprofloxacin. Here, the IWW auditors were able to detect a wastewater concentration of >10 µg/l, which **exceeds the contractually agreed threshold value by an alarming 11,000 per cent** (Figure 1). The other threshold value exceedances in the production wastewater were also in the order of several thousand per cent. For levofloxacin, for example, a concentration of 7.3 µg/l was found, **an exceedance of almost 2,800 per cent**.

These exceedances are very worrying.

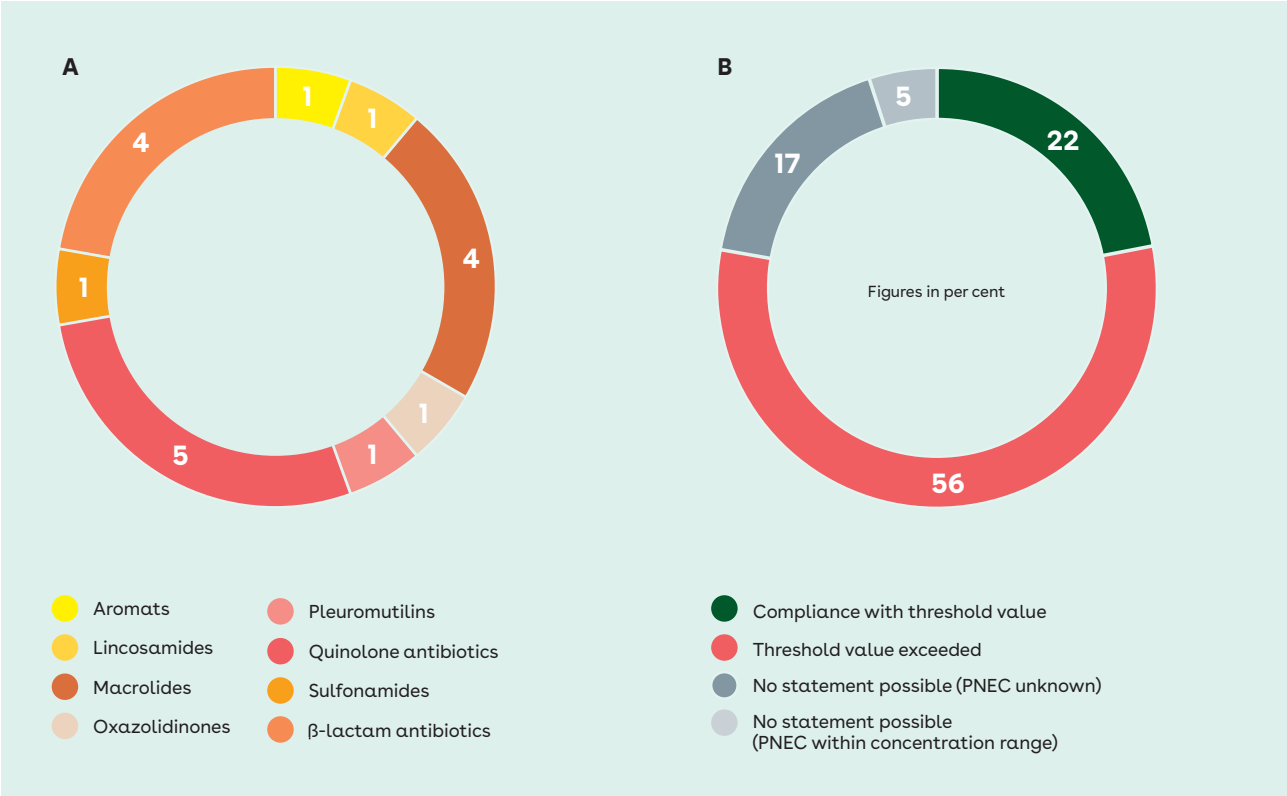
Despite the comparable magnitude of the measured concentration of ciprofloxacin and levofloxacin, the clear difference in the percentage exceedance is due to the effect-based, different threshold values. This is because a supposedly low concentration does not allow any direct conclusions to be drawn about possible environmental effects, particularly in the case of substances that may be highly effective, such as antibiotics.

Alarmingly high concentrations of antibiotics were also detected in the surrounding environment in the waters affected by the production sites (Figure 1).

Figure 1: Threshold exceedances of investigated antibiotics

Illustration of the measured maximum concentrations and threshold value exceedances (as a percentage exceedance of the PNEC) of the contracted antibiotics in production wastewater and environmental samples, as well as conspicuous antibiotic concentrations in environmental samples.

Figure 2: Antibiotics in environmental samples



A: Number of antibiotics per group; B: Threshold value exceedances of antibiotic detections.

In several cases, the waters sampled flow through heavily utilised pastureland and inhabited settlements.

A total of 18 different antibiotics from eight groups were detected in these environmental samples by the investigators (Figure 2A).

Alarming results

In the total number of measurements of the environmental water samples, more than 50 per cent of the antibiotic samples detected exceeded the PNEC as an ecotoxicologically relevant threshold value, while for other antibiotics such a reliable, scientifically derived effect threshold value is completely lacking (Figure 2B).

Of the nine water bodies sampled, the environmental sample with the most antibiotic findings measured (10 in total) came from a European stream. This is a watercourse that not only runs directly through various settlements but is also used by the local population for local recreation and fishing, for example.

The environmental sample with the highest exceedance of a threshold value was taken from a body of water that originates from the rainwater overflow of an Indian production facility. This body of water runs directly through an area used for cattle grazing. **The water concentration of azithromycin measured here exceeds the ecotoxicologically relevant threshold value by at least 1,600,000 per cent (!).**

All in all, the initial results of this study and the measured exceedances pose a risk, and not only to the local population and environment; antimicrobial resistance can spread worldwide in a short space of time as a result of tourism, work-related travel and globalised trade.[6]

The results of the pilot study so far confirm the findings of an investigative study conducted by the media organisations NDR, WDR and Süddeutsche Zeitung in collaboration with infectious disease specialists from Leipzig University Hospital in 2017.

This study had detected a concentration of antibiotics in the environment around production facilities in India that exceeded the threshold value above which resistance can develop by a factor of 5,500.1.[7]

In 2007, Larsson and colleagues had already found extremely high concentrations of antibiotics in the wastewater of pharmaceutical manufacturers, which exceeded the toxic levels for some bacteria by a factor of 1,000.[8]

Pilot study shows positive effects: Increased knowledge and change could be achieved at some manufacturing sites

In general, the inspections carried out so far show a differentiated picture of the production sites. Both exemplary facilities with successful wastewater management and outdated and sometimes environmentally hazardous facilities have been inspected.

However, the first positive effects of the inspections have also been recorded in the almost two-year investigation period. One of the Indian production facilities inspected, for example, has already increased and adapted its wastewater treatment, which had a positive effect on a previously identified exceedance of the maximum concentration of the contracted antibiotic. While an initial concentration of 10 µg/l was measured during the initial inspection, the active substance was no longer detectable in a follow-up sampling after the adaptation measures had been implemented. Another Indian production facility optimised the storage and recycling of spills following a visit by representatives of the IWW. As a result of the study, a more conscious and therefore more sustainable approach to antibiotics was established at this production facility. Plans are now being made to change the wastewater treatment in other production sites.

Thanks to the sampling and the direct dialogue with the representatives of the IWW on site, knowledge about the environmentally critical and health-endangering effects of production has been demonstrably expanded. Raising awareness of this issue has already led to local improvements in the treatment of production wastewater. ←

Need for action

The results of the pilot study so far clearly show the great need for action at national and, above all, European level. This is even more important because the study partners have so far only been able to shed light on a section of pharmaceutical production and have presumably only seen the "tip of the iceberg". If the international community wants to get to grips with the problem of antibiotic resistance and reduce the associated negative consequences for the environment and health in order to effectively avert negative consequences for the environment and health, regulatory parameters must start at the root. **To effectively minimise the risks to the environment and health, we need a European approach** that can bring the full weight of the European market to bear. This requires a united and strong German presence on the European stage. It is therefore important that existing windows of opportunity, such as the current revision of EU pharmaceuticals legislation, are utilised in a targeted manner to strengthen the sustainable supply of pharmaceuticals. **Now is the time to act so that antibiotic resistance and subsequently rising healthcare costs can be avoided in the future.** ←

Need for political action

A regulatory concept is needed for a sustainable supply of pharmaceutical products with regard to all three aspects of sustainability

A functioning, reliable and future-proof supply of pharmaceuticals must be designed taking into account all three aspects of sustainability – ecological, social and economic. In this context, the ecological impact must be considered in order to prevent consequential damage to the health of people, such as an increasing number of antibiotic resistances. At the same time, the social impact of guaranteed access to safe and high-quality care and the economic impact of efficient and future-oriented use of available financial resources must be taken into account.

1 Strengthening ecological sustainability through binding environmental criteria for the manufacture of pharmaceutical products and their control within and outside Europe

Antimicrobial resistance must be effectively combated so that antibiotics can continue to be effective and people and the environment are successfully protected from the dangers that arise during production.

There are extensive efforts at global, European and national level to reduce and prevent aspects subject to regulation.[9, 10, 11] However, production-related environmental pollution has not yet been the focus of political discourse. An analysis by the UN Environment Programme (UNEP) shows that a reduction in environmental pollution in bodies of water would significantly reduce the risk of multi-resistant germs.[12] In particular, the report emphasised the pollution caused by wastewater from the pharmaceutical industry.

The joint findings of the pilot study demonstrate the great need to implement extended authorisation criteria and control mechanisms. The pilot study shows that it is possible to integrate environmental criteria into the supply of pharmaceutical products. However, national approaches are reaching their limits and are not expedient in view of the limited buying power of the German pharmaceutical market amounting to just four per cent.[13] Nevertheless, additional initiatives at European level are therefore needed to introduce and monitor binding environmental criteria for the production of pharmaceuticals within and outside Europe.

Inclusion of binding environmental criteria in EU pharmaceutical legislation

In the manufacture of pharmaceutical products, there is a risk of contaminated production wastewater and surface runoff being released into the environment. To ensure that the production of pharmaceuticals no longer takes place at the expense of the environment and health in future, both **scientifically derived threshold values for active substance emissions into the environment** at the production site as well as **binding environmental criteria for the authorisation and ongoing production of selected pharmaceutical products, in particular antibiotics**, are required. The threshold values for the production of pharmaceuticals must be enshrined in EU pharmaceutical legislation in the form of emission specifications.

Establishment of standardised control systems
In addition, standardised control systems are required to effectively verify compliance with the environmental criteria for obtaining a marketing authorisation and ongoing production. Pharmaceutical manufacturers must be obliged to submit corresponding **audit and certification protocols**, which they **must provide evidence of in order to be awarded public contracts**. The legal basis for this must first be created in EU pharmaceutical legislation. The corresponding regulations should be based on the well-known and proven guidelines of Good Manufacturing Practice (GMP) and contain, among other things, specifications for an auditor, staff training in accordance with corresponding guidelines and protocol templates for clients. It would be desirable for specific inspection organisations to be established and for their powers, such as unannounced inspections, to be clearly defined.

Knowledge transfer through partner projects, particularly in the Asia region
Irrespective of the legal requirements in EU pharmaceutical legislation, the development of control systems and technical equipment on site to improve the production process must be promoted. This requires a **transfer of knowledge** through the establishment of **partnership projects, particularly with the Asian region**, which plays a prominent role in the production of active substances.

2 Social sustainability through the stabilisation of supply chains and stockpiling

Pharmaceutical manufacturing is a large global network with complex and global supply chains. In our globalised world, it will not be possible to fully regionalise these pharmaceutical value chains, which is why it is even more important to use effective mechanisms to make supply more resilient.

Stabilising supply chains by amending EU procurement law
To date, European law has not allowed privileges to be granted on the basis of geographical criteria in public tenders. A corresponding attempt by the AOK to include the supply chain and thus the geographical origin of the pharmaceutical product as a criterion in the tendering process for pharmaceuticals was declared by the German supreme court for public procurement law to be incompatible with EU public procurement law. The diversification of supply chains for antibiotics attempted at national level as part of a recent law to combat supply shortages and improve the supply of pharmaceuticals also fails to effectively shorten supply chains, as free trade agreements mean that "Made in EU" pharmaceuticals can also come from Hong Kong or New Zealand, for example. To avoid environmentally harmful transport routes, secure supply and promote Europe as a business location, EU public procurement law needs to be amended to define the place of production as a permissible award criterion. This increases the resilience of supply chains and promotes production close to supply. This should be flanked by economic policy measures to **promote production sites in the EU**.

Expansion of the early warning system for the early detection of imminent supply shortages for pharmaceuticals and further strengthening stockpiling
Whether antipyretics, cancer drugs, antibiotics or psychotropic drugs, supply shortages have been a global problem for many years and cannot be solved by price alone. Supply bottlenecks occur to an even greater extent in countries with a higher price level than in Germany (e.g., Switzerland or the USA). A **comprehensive early warning system** for all pharmaceuticals along the entire value chain is absolutely essential. This means that suppliers, pharmaceutical companies, wholesalers, and pharmacies must all be included. This also applies to **stockpiling**. It is incomprehensible that non-discounted pharmaceutical products are excluded from the new stockpiling regulations, when it is precisely in this area that delivery failures are higher than for pharmaceutical products subject to discount contracts.

3 Economic sustainability through continuous further development of pharmaceutical discount contracts

The measures described above not only help to improve the protection of the environment and people's health as well as the supply of pharmaceutical products, but also contribute to **strengthening Europe as a business location. In future, no pharmaceuticals produced to the detriment of the environment and human health should be allowed to be placed on the market in Europe**. This prevents unequal treatment of production in Europe compared to non-European production and leads to a fair competitive situation. At the same time, it creates an economic incentive to establish and expand a suitable pharmaceutical industry in Europe and promotes the diversification of pharmaceutical production.

In Germany, discount contracts with pharmaceutical companies make an important contribution to a high-quality, stable and at the same time economical supply of pharmaceuticals. Contrary to what is often claimed, they are not the cause of supply shortages, but guarantee a more reliable supply. **Supply shortages occur much less frequently for pharmaceuticals for which a discount contract exists than for pharmaceuticals without discount contracts**. According to statutory health insurance data for 2021, supply shortages in the supply of discount pharmaceuticals were 1.2 per cent, while 4 per cent of medicines were not available in the off-patent „non-contract market".

Discount contracts stabilise supply chains and counteract shortages:

- Pharmaceutical discount contracts have a term of two years. This creates planning security for the contract partners.
- Pharmaceutical manufacturers are obliged to maintain several months' supply (stockpiling).
- Smaller and medium-sized pharmaceutical companies only gain effective access to the market through discount contracts. Discount contracts therefore demonstrably contribute to supplier diversity.

Discount contracts and other cost-effectiveness instruments such as reference prices or the price moratorium protect contributors from excessive pharmaceutical prices and ensure the financial performance of the statutory health insurance. For all these reasons, discount contracts must not be weakened, but must be retained as an important instrument of statutory health insurance and as explained, continuously developed with a view to the ecological and social dimension of sustainability. **It also became clear that the effect of the successful instrument of pharmaceutical discount contracts is limited with regard to the global challenges identified in the ecological and social dimension of sustainability**. The problem of antimicrobial resistance in pharmaceutical production cannot be tackled solely with this instrument, nor can supply chains be diversified solely with discount contracts. Solutions are needed via European pharmaceutical and authorisation law as well as economic policy measures at national and European level. ←

Concrete political demands

Inclusion of binding environmental criteria in EU pharmaceuticals legislation

- **Scientifically based upper limits for active substance emissions into the environment** (active substance inputs from manufacturing sites into water, soils and other environmental compartments)
- **Binding environmental criteria for the authorisation and ongoing production** of selected pharmaceutical products, in particular antibiotics
- In the course of the current **amendment of EU pharmaceuticals legislation**, environmental criteria for production must be specified

Standardised control systems to check compliance during authorisation and ongoing production

- **Introduction of standardised control systems** for compliance with the environmental criteria for authorisation and ongoing production
- **Obligation of pharmaceutical companies** to submit corresponding **audit and certification protocols when awarding public contracts and creation of the corresponding legal basis, especially in EU pharmaceuticals and EU procurement law**
- Orientation towards the well-known and proven guidelines of Good Manufacturing Practice (GMP): including specifications for an auditor, staff training in accordance with corresponding guidelines and protocol templates for contracting bodies
- Designation of specific control institutions in EU pharmaceuticals legislation and their room for manoeuvre, e.g., unannounced inspections

Knowledge transfer through partner projects, particularly in the Asia region

- Strengthening of the development of control systems and technical equipment on site to improve the production process
- Establishment of **partnership projects, particularly with the Asian region**

Shortening of supply chains by amending EU public procurement law

- Amendment of Directive 2014/24/EU of the European Parliament and of the Council of 26 February 2014 on public procurement to include the place of production as an award criterion
- Furthermore, additional and complementary **economic policy measures are needed to promote business locations in the EU**

Expansion of the early warning system for recognising impending supply shortages for pharmaceutical products and further strengthening stockpiling

- A comprehensive early warning system for all pharmaceuticals along the entire value chain is absolutely essential
- All parties involved – from suppliers, pharmaceutical companies and wholesalers to pharmacies – must be included
- Extension of the stockpiling-regulations under ALBVVG to non-discounted drugs

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